Myeloid Malignancies: The Journey from Basic Molecular Biology to Clinical Application

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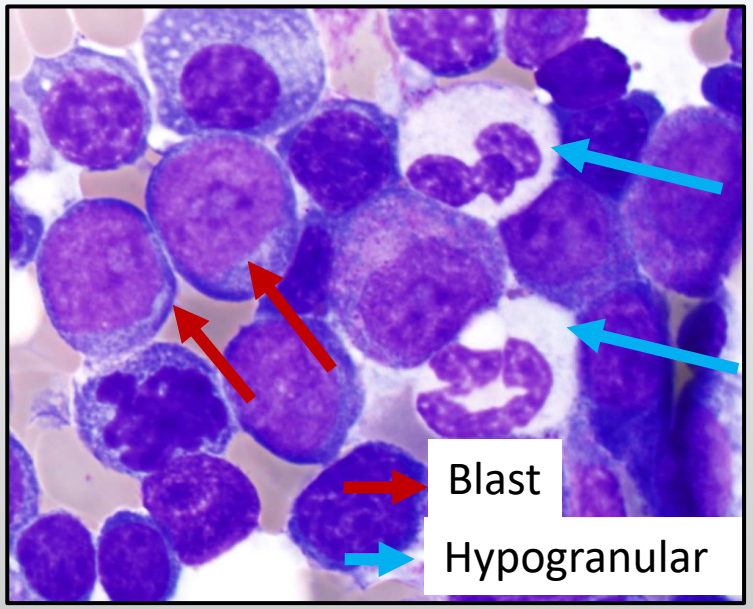
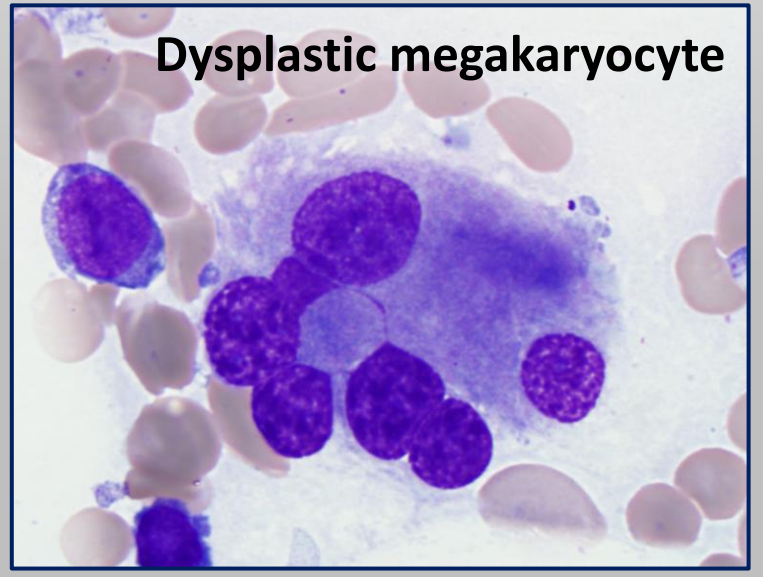
MYELODYSPLASTIC SYNDROMES (MDS)

- **Clonal** hematopoietic stem cell disease
  - myeloid **malignancy** [*WHO 9980/3]*
- Ineffective, **dysplastic hematopoiesis** with **<20% blasts** in bone marrow resulting in:
  - **Anemia,** and/or **Thrombocytopenia,** and/or**Neutropenia**
- **Transforming potential** to secondary acute myelogenous leukemia (**sAML**)
- **Prevalence**: 10-20% therapy-related, 80-90% de novo, 30,000 cases per year US.
- Increased recognition of germline predisposition particularly for pediatric and younger adult patients.





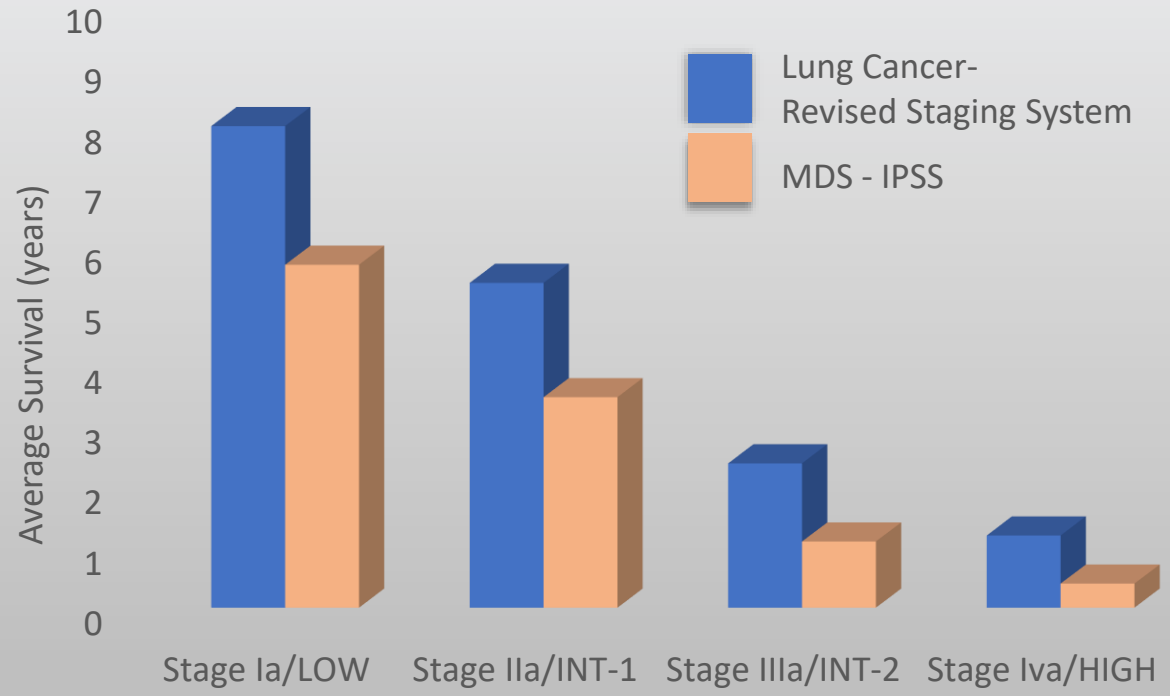
BM morphology courtesy of Dr. Katherine Calvo

MDS PROGNOSIS AND THERAPY

- 1/3 die of pancytopenia
- 1/3 transform to AML
- 1/3 die of unrelated causes

- Genetics drives the disease
  - del 5q survival >7 yrs
  - TP53 mutations <1 yr

Supportive Care
Erythroid Stimulating Agents (ESA)
Hypomethylating Agents (HMA)
Lenalidomide
Luspatercept
*Allogeneic Hematopoietic Stem Cell Transplant (HSCT)



Steensma DP. **Leuk Lymphoma**. 2016;57(1):17-20.

Greenberg, et al. **Blood**. 1997; Adebonojo et al. **Chest**. 1999

BARRIERS TO PROGRESS

- Limited understanding of disease biology and dearth of animal and cellular models - no cell lines, no robust xenografts.
- No developed methods and definitions of measurable residual disease to guide therapies.
- Many patients are elderly with comorbidities.

Why study MDS at the NIH intramural program?

- Recalcitrant cancer, rare disease, lack of progress in therapy over the last 15 years.
- Unique disease model to study *in situ* evolution of cancer from inflammation, genetic defects to manifest disease.
- Science waiting to be translated from the intramural program.
- Subacute clinical course suitable for outpatient management.
- Opportunity to study MDS in a coordinated, multi-institute approach across protocols and in both children and adults.
- Nucleate activity in both intramural and extramural communities, convene the broader MDS scientific community, mobilize resources for trials, biomarker development, preclinical models.
- Opportunity to study natural history of inherited leukemia (RUNX1, GATA2) - help inform timing of HSCT.

NIH Myeloid Malignancies Program

Mission -- to develop a comprehensive program aimed at understanding and treating myeloid malignancies in children and adults.

Vision -- to successfully control, cure, and ultimately prevent MDS and AML.

History

2018: exploratory seminar series
2019: organizational planning and establishment of milestones
2020: MMP established as a program in 2020
2021 – present: recruitment of staff

Theme 1: Post-transcriptional regulation in MDS/AML.
Theme 2: Germline predispositions to myeloid malignancy.
Theme 3: Pre-clinical models to study MDS biology and therapy.
Theme 4: Role of the immune system in control of MDS/AML.

NIH Myeloid Malignancies Program

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(NCI-CCR/ID-CTP)

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co-chair (NCI-CCR/LRBGE)

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Lori Wiener, PhD, DCSW, LCSW-C (NCI-CCR/POB)

Somatic Mutations in Myelodysplasia

DNA methylation	Chromatin / Transcription	Splicing/ RNA processing	Translation	Tumor Suppressors	Signaling
DNMT3A	*ASXL1*	*SRSF2*	*?*	*TP53*	*FLT3-ITD*
TET2	*BCOR*	*U2AF1*		*PHF6*	*FLT3-TKD*
IDH1	*BCORL1*	*SF3B1*			*NRAS*
IDH2	*EZH2*	*ZRSR2*			*KRAS*
WT1	*KDM6A*				*PTPN11*
	KMT2A				*CBL*
Cohesin / CTCF	*DHX29*				*JAK2*
					NF1
STAG2	*RUNX1*				*CSF3R*
SMC1A	*NPM1*				
SMC3	*CEBPA*				
RAD21	*ETV6*				
CTCF	*GATA2*				

- MDS is a disease of abnormal myeloid differentiation.
- AML is a disease of abnormal myeloid differentiation + proliferation.
- Splicing factor mutations account for ~ 50% of MDS patients.

Theme 1: Post-transcriptional regulation in MDS/AML.

The spliceosome is…

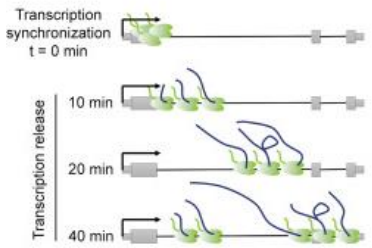
… a ribonucleoprotein complex composed of > 200 proteins and RNA.

… responsible for generating mRNA which is translated into protein.

… a single-turnover enzyme.

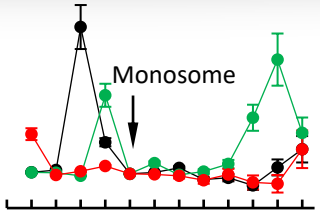
… frequently mutated in myeloid malignancies (MDS, AML).

Spliceosome mutations: bench to bedside to bench

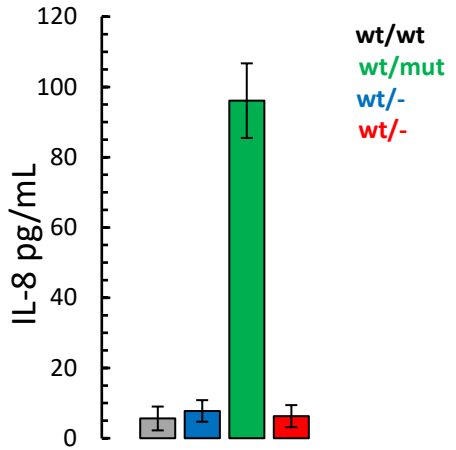


Development of cutting-edge approaches for understanding splicing.

U2AF1 has a non-canonical role in translation regulation.



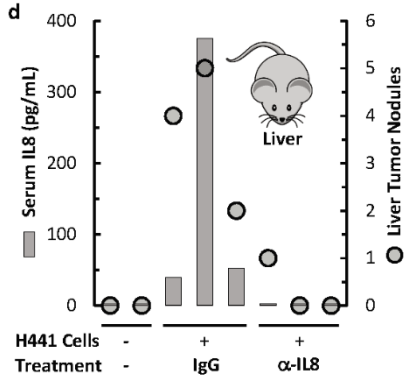
Translation fraction #



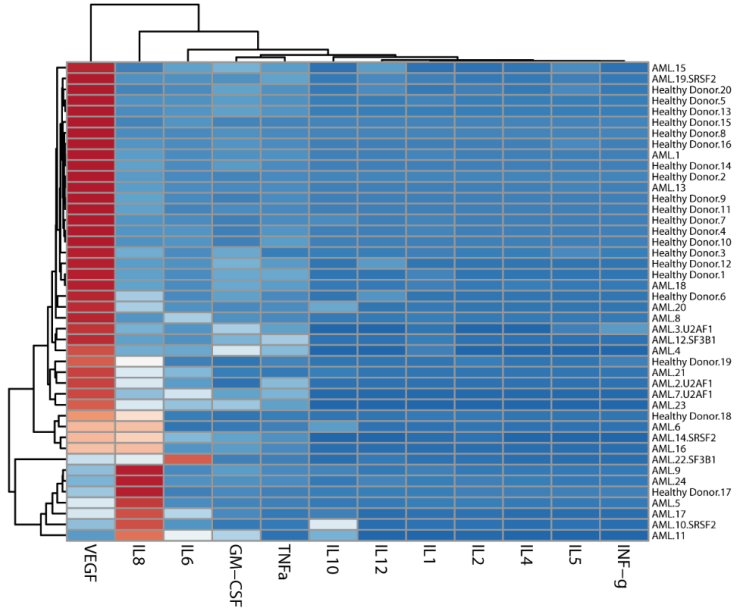
One target: <u>interleukin 8</u>

<u>Bristol-Myers Squibb Humax IL-8</u>
Approval for pre-clinical studies: Oct, 2019
Approval for clinical trial at NIH: June, 2020
FDA IND: September, 2021

Blocking IL-8 reduces tumor burden in a xenograft model.



Relapsed/ refractory AML patients: > 30% with splicing factor mutations and also show high levels of IL-8.



Rodriguez, **Cell**, 2109; Palangat, **Genes and Development** (2019); Akef, **PLoS Biology** (2020); Wan, **Cell**, 2021

Theme 2: Germline predispositions to myeloid malignancy.

Natural History and Biospecimen Acquisition Protocol for Myelodysplastic Syndromes, PI McGraw, CCR, NCI

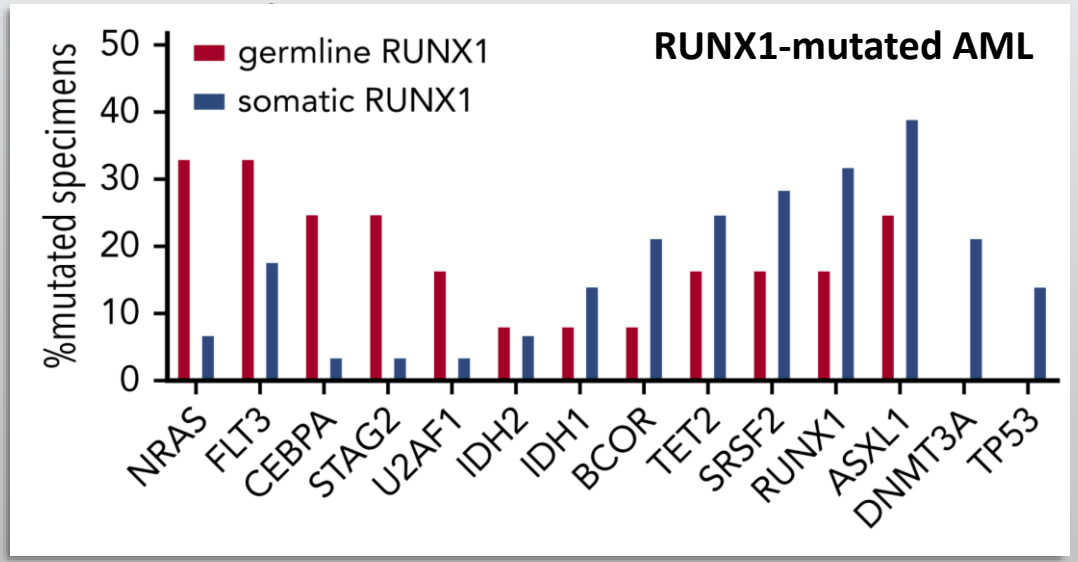
CHIP/CCUS Natural History Protocol, PI Groarke, NHLBI

Allogeneic HSCT for GATA2 Deficiency, PI Arnold, CCR, NCI

Longitudinal Studies of patients with FPDMM & Germline RUNX1 mutations, PI Liu, NHGRI

Phase Ib Study of Imatinib to Increase RUNX1 Activity in Patients with Germline RUNX1 Deficiency, PI Cunningham CCR, NCI

Familial platelet disorder with associated myeloid malignancy (FPDMM)

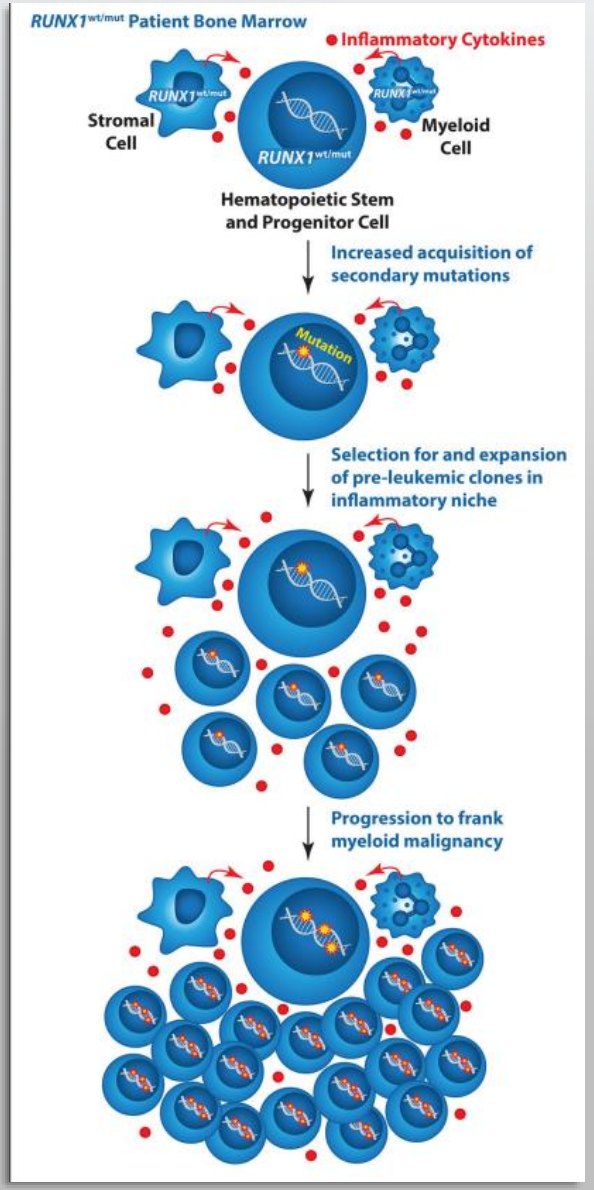


Simon, **Blood**, 2020.

Hypothesis:

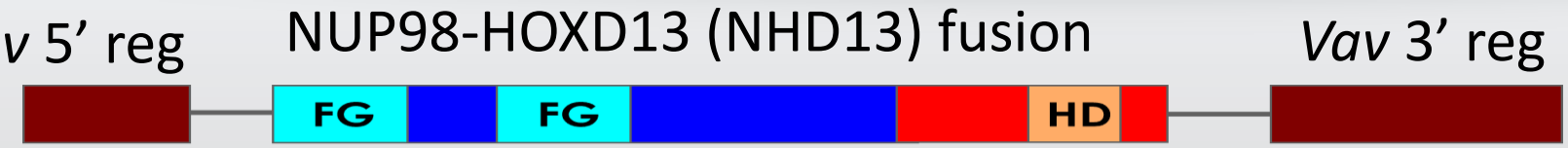
Imatinib can **enhance WT RUNX1** protein activity in RUNX1 deficiency patients potentially improving megakaryocyte dysplasia, thrombocytopenia, platelet dysfunction and auto- inflammatory components of this disorder as compared to NIH RUNX1 natural history data.

This mechanism **may also decrease the acquisition of secondary somatic mutations** and slow or prevent the development of MDS/AML in affected individuals.



Bellissimo, **Front Cell Dev Biol**. 2017

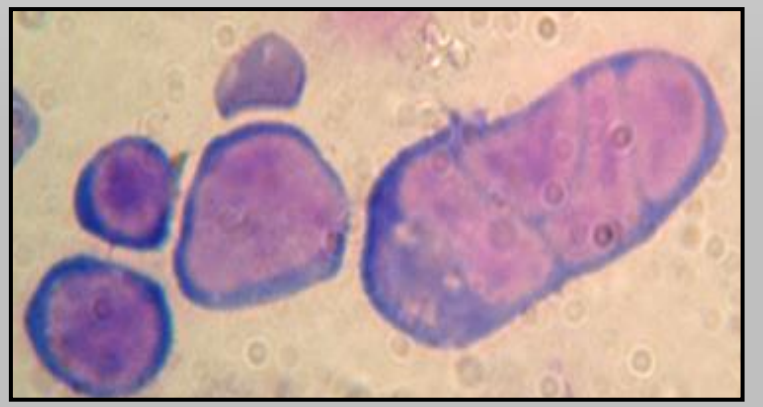
Theme 3: Pre-clinical models to study MDS biology and therapy.



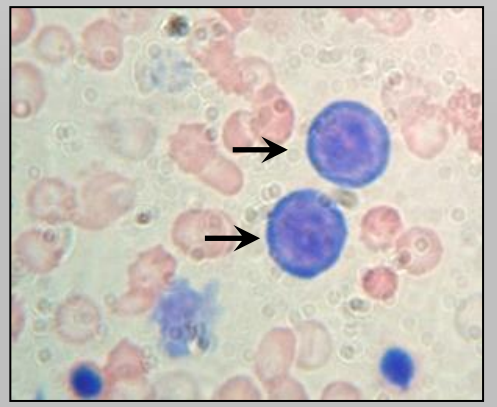
vavNHD13 mice develop MDS:

- Cytopenia
- Transformation to AML
- Widely distributed, >20 academic labs
- Four commercial licensees.
- Used to provide pre-clinical evidence for development of luspatercept (only new FDA approval for MDS in past 15 years).

	WBC (10^9/L)	Neutrophil (10^9/L)	Hb (g/dL)
NHD13 (n = 22)	1.8	0.44	11.9
Control (n = 7)	6.5	1.4	14.2
p value	<0.001	<0.001	<0.001



multinucleate erythroblasts



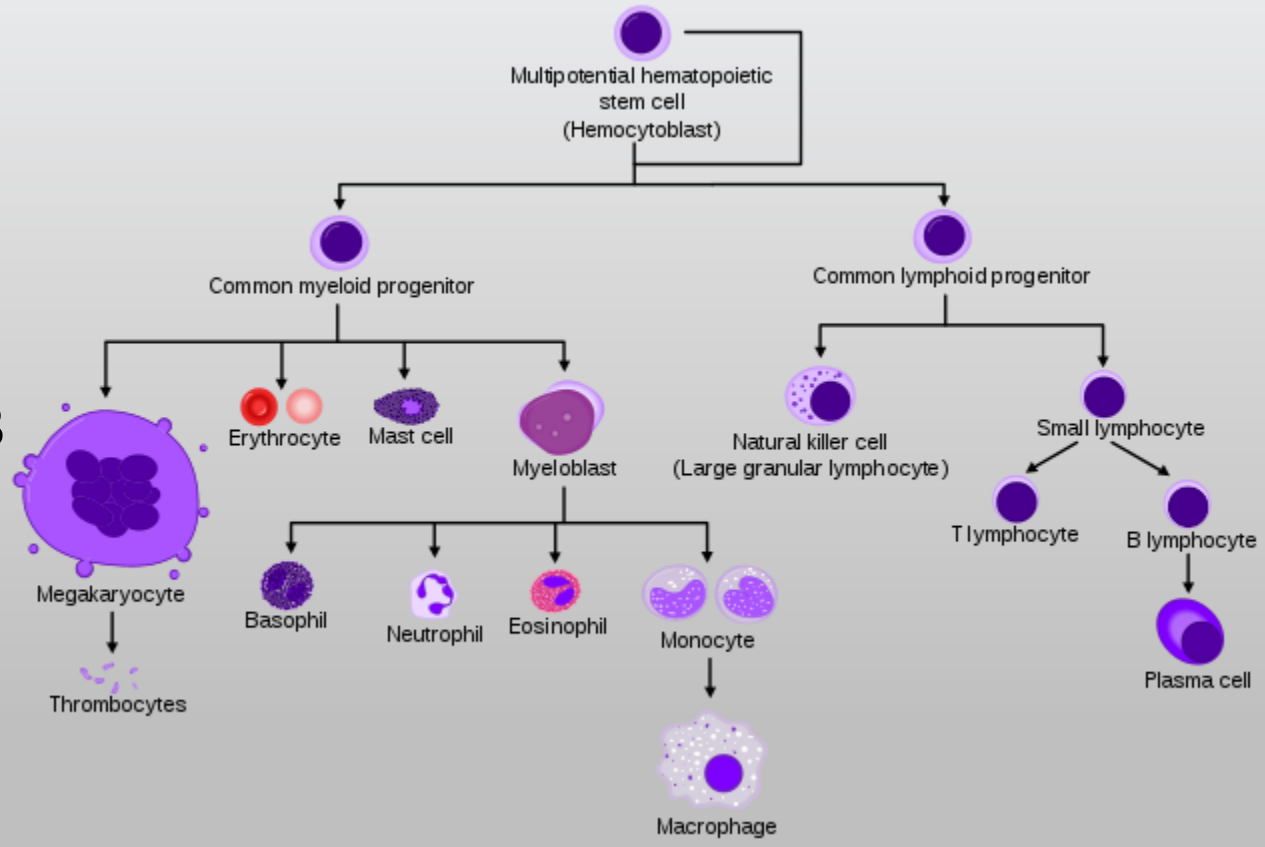
AML blasts

Lin, **Blood**, 2005; Slape, **JNCI**, 2008; Suragani**, Nat Med**, 2014; Chung, **PLoS One**, 2017

Theme 4: Role of the immune system in control of MDS/AML.

First in human, first in child: CD33 CAR T-cell:

- Preclinical data demonstrate therapeutic potential of targeting CD123 and CD33.
- Majority of childhood AML expresses CD123 and/or CD33.
- CD33 is perhaps a ‘less risky’ first CAR T cell target given clinical experience with GO.
- Bright CD33 expression in many highest-risk patients.



Nirali Shah, ClinicalTrials.gov NCT03971799

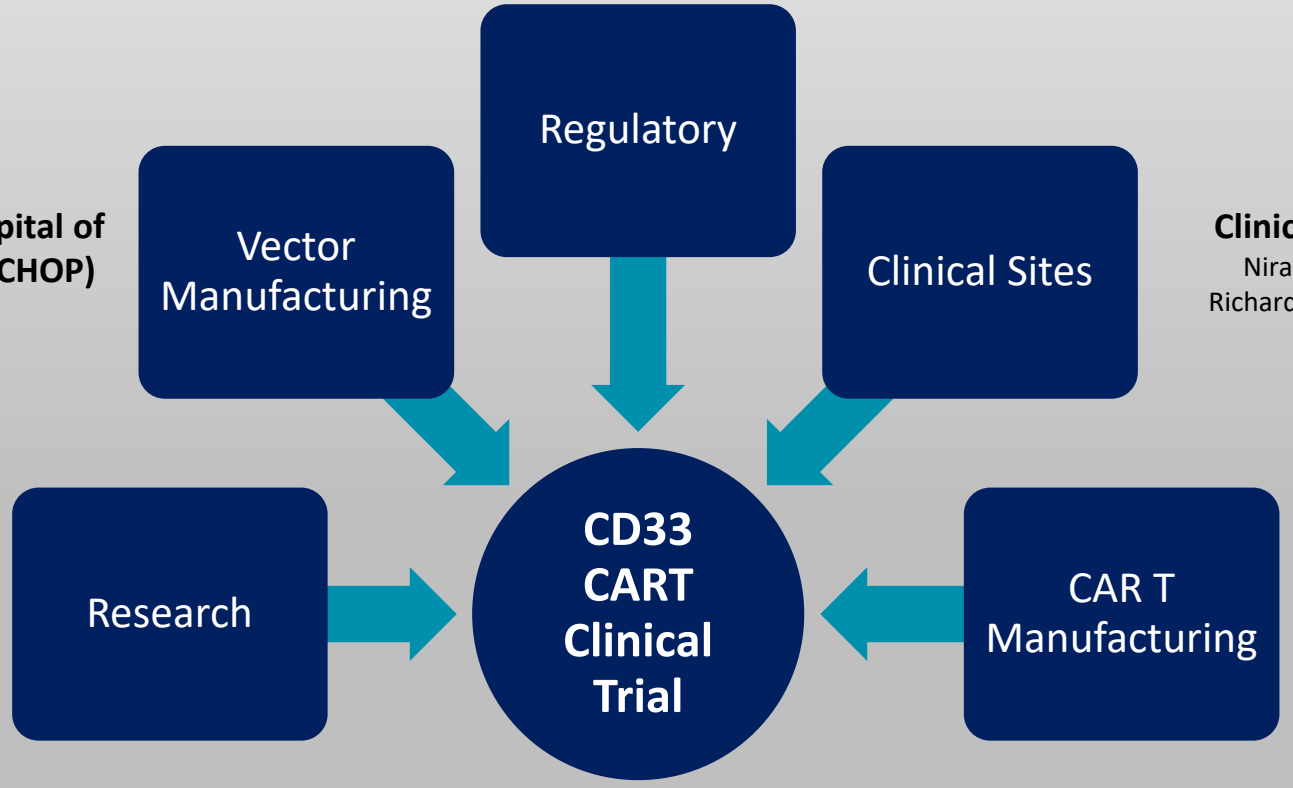
Theme 4: Role of the immune system in control of MDS/AML.

Clinical Trial IND:
Pediatric Blood and Marrow Transplant Consortium (PBMTC)
with Resource for Clinical Investigation in Blood and Marrow Transplantation (RCI BMT)
Center for International Blood and Marrow Transplant Research/ National Marrow Donor Program (CIBMTR / NMDP)

IND coordination:
Hati Kobusingye, MS (NMDP)

Clinical Trial Service Leads:
Erin Leckrone, MD (RCI BMT)
Steve Devine, MD (RCI BMT)

Children's Hospital of Philadelphia (CHOP)



Clinical Trial Co-PIs:
Nirali Shah, MD (NCI)
Richard Aplenc MD (CHOP)

CD33CART Inventors:
Terry Fry, MD (UColorado)
Sarah Tasian, MD (CHOP)

NCI BDP:
Anthony Welch, PhD (NCI COR)
George Mitra, PhD (BDP PI)

Nirali Shah, ClinicalTrials.gov NCT03971799

NIH Myeloid Malignancies Program: Present and Future

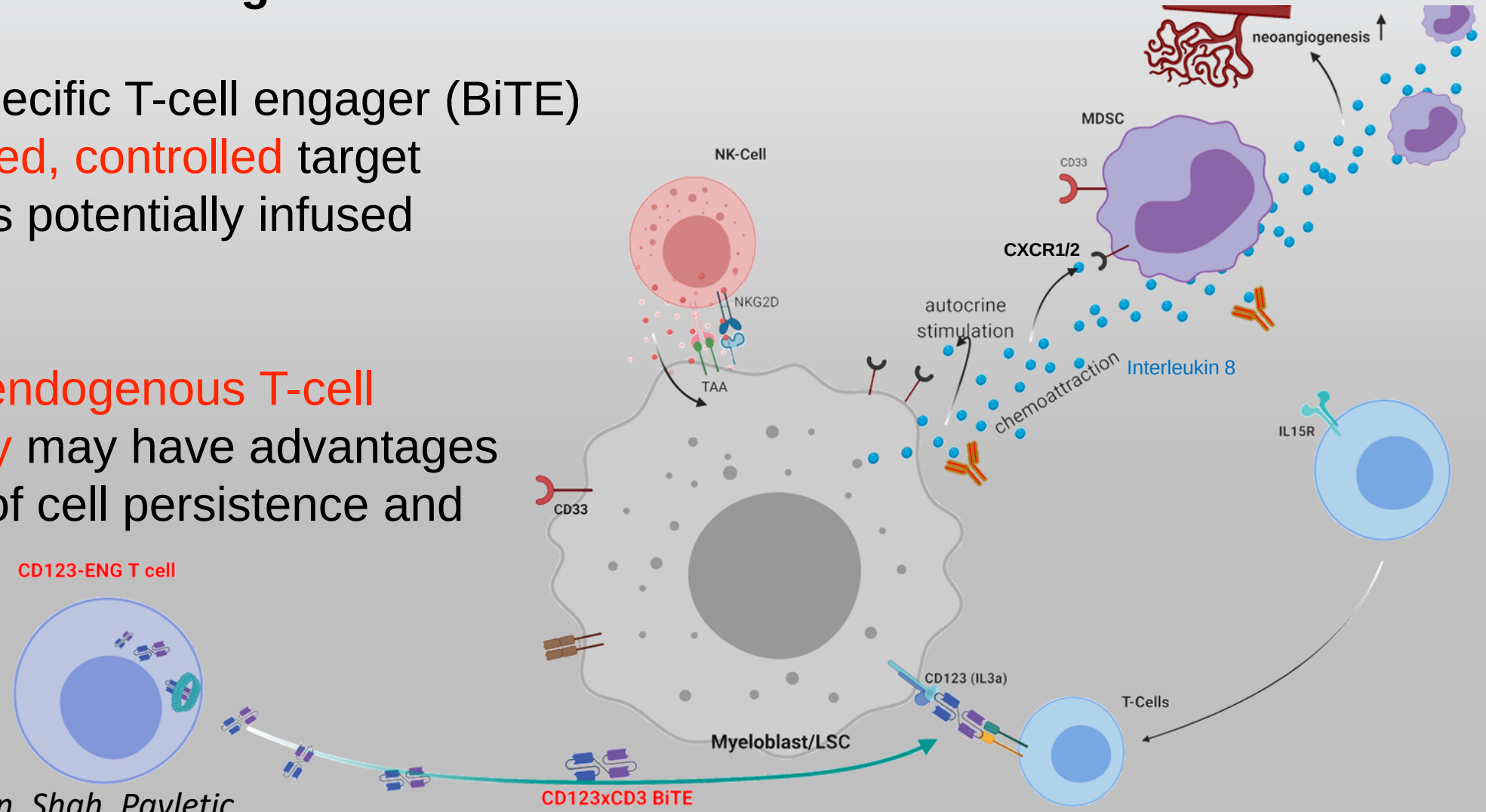
- Formation of an MDS/AML clinic as a site for studying the disease presentation, biology, develop assessment tools and pursue enrollment on clinical therapy protocols.
- Recruitment of a clinical/translational team:
  - Physician scientists, clinical research fellows, staff clinicians, research nurses.
- Development of clinical trials:
  - Phase 1/2 Study of Anti-CD33 Chimeric Antigen Receptor-Expressing T Cells (CD33CART) in Children and Young Adults with Relapsed/Refractory Acute Myeloid Leukemia (**NCT03971799**)
  - Natural History and Biospecimen Acquisition for Myelodysplastic Syndromes (**NCT05350748**)
  - A Phase I/II Trial of BMS-986253 in Myelodysplastic Syndromes (**NCT05148234**)
- Increasing involvement of basic scientists:
  - Recruitment of basic science investigators through the intramural Stadtman process.
  - Engaging existing investigators from relevant fields.

NIH Myeloid Malignancies Program: Present and Future

CD123xCD3 BiTE-secreting T cells First-in-class

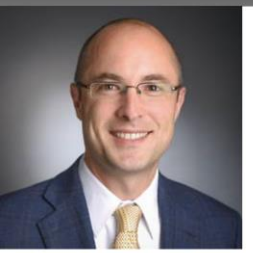
Secretion of bispecific T-cell engager (BiTE) allows for localized, controlled target killing with T cells potentially infused at a lower dose.

Preservation of endogenous T-cell activation biology may have advantages in maintenance of cell persistence and homeostasis.



Bonifant (JHU), Holtzman, Shah, Pavletic

Co-PIs



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NIH National Heart, Lung, and Blood Institute

Chris Hourigan DM DPhil

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Jerry Radich MD

MRD in AML Project

Advancing opportunities for patients with acute myeloid leukemia

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MOLECULAR EVALUATION OF AML PATIENTS AFTER STEM CELL TRANSPLANT TO UNDERSTAND RELAPSE EVENTS

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Anticipated launch August 2022

NIH Myeloid Malignancies Program

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